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Title: **NOVEL COMPOUNDS**

Reference: F 2019

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NOVEL COMPOUNDS

The present invention relates to certain thiazolopyrimidine compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

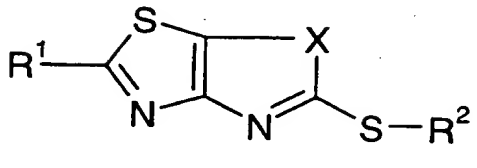
Interleukin-8 (IL-8) which is sometimes referred to as polymorphonuclear (PMN) chemotactic factor, monocyte-derived neutrophil-activating peptide (MONAP), monocyte-derived neutrophil chemotactic factor (MDNCF), T lymphocyte chemotactic factor (TCF), lymphocyte-derived neutrophil-activating peptide (LYNAP) and neutrophil-activating peptide 1 (NAP-1) is a chemoattractant for neutrophils, basophils and a subset of T-cells and is produced by a wide variety of tissues and cells including mononuclear phagocytes, endothelial cells, fibroblasts, epithelial cells and alveolar macrophages.

Two high affinity human IL-8 receptors (77% homology) have been characterised: IL-8Rα (CXCR1), which binds only IL-8 with high affinity, and IL-8Rβ (CXCR2), which has high affinity for IL-8 as well as the chemokines GROα, GROβ, GROγ and NAP-2 (see Holmes *et al.*, *Science* (1991) 253, 1278; Murphy *et al.*, *Science* (1991) 253, 1280; Lee *et al.*, *J. Biol. Chem.* (1992) 267, 16283; LaRosa *et al.*, *J. Biol. Chem.* (1992) 267, 25402; and Gayle *et al.*, *J. Biol. Chem.* (1993) 268, 7283).

As IL-8, GROα, GROβ, GROγ and NAP-2 promote the accumulation and activation of neutrophils, these chemokines have been implicated in a wide range of acute and chronic inflammatory diseases such as psoriasis and rheumatoid arthritis.

Thus, it would be desirable to develop compounds that are antagonists of the IL-8α (CXCR1) or IL-8β (CXCR2) receptor which could be used to treat inflammatory diseases associated with an increase in chemokine production and consequential chemotaxis of neutrophils into the inflammatory site.

In accordance with the present invention, there is therefore provided a compound of general formula



(I)

wherein R^1 represents a hydrogen or halogen atom, or a group $-NR^3R^4$;

R^3 and R^4 each independently represent a hydrogen atom, a C_3-C_6 cycloalkyl group, or a C_1-C_6 alkyl group optionally substituted by one or more substituents independently selected from amino (NH_2), amido ($-C(O)NH_2$), hydroxyl (-OH), (di)C_1-C_6 alkylamino, C_2-C_6 acylamino, C_1-C_6 alkoxy optionally substituted by at least one hydroxyl, and morpholinyl;

R^2 represents a C_1-C_6 alkyl or C_2-C_6 alkenyl group, each of which may be optionally substituted by a phenyl or phenoxy group, the phenyl or phenoxy group being optionally substituted by one or more substituents independently selected from halogen atoms, nitro, trifluoromethyl, C_1-C_6 alkyl, C_1-C_6 alkoxy and phenoxy;

X represents a group $-C(O)NH-$ or $-C(NR^5R^6)=N-$; and

R^5 and R^6 each independently represent a hydrogen atom, a saturated hydrocarbyl ring system containing from 3 to 7 carbon atoms optionally substituted by at least one hydroxyl group, or a C_1-C_6 alkyl group optionally substituted by one or more substituents independently selected from the group consisting of amino, hydroxyl, C_1-C_6 alkoxy optionally substituted by at least one hydroxyl, C_1-C_6 alkylthio, (di)C_1-C_6 alkylamino optionally substituted by at least one hydroxyl, and phenyl optionally substituted by one or more substituents independently selected from halogen atoms, amino and hydroxyl; or R^5 and R^6 together with the nitrogen atom to which they are attached form a pyrrolidinyl or piperidinyl ring optionally substituted by one or more substituents independently selected from hydroxyl, hydroxyC_1-C_6 alkyl and benzyloxycarbonyl; or

a pharmaceutically acceptable salt or solvate thereof.

In the context of the present specification, unless otherwise indicated, an alkyl or alkenyl group or an alkyl or alkenyl moiety in a substituent group may be linear or branched. Where a substituent in an alkenyl group is a phenoxy group, the phenoxy group is not attached to an unsaturated carbon atom. Further, the alkyl moieties in a di-C_1-C_6 alkylamino group may be the same or different and where the (di)C_1-C_6 alkylamino is optionally substituted by at least one hydroxyl group, the hydroxyl group(s) will be attached to the alkyl moiety or moieties. Moreover, it should be understood that the group X is oriented in the ring such that the NH or =N moiety of X is bonded to the same carbon atom as the group S-R^2.

In formula (I) above, the group R^1 represents a hydrogen or halogen atom, or a group -NR^3R^4. Particularly advantageous compounds of formula (I) are those in which R^1 represents a group -NR^3R^4.

Preferably R^3 and R^4 each independently represent a hydrogen atom, a C_3-C_6 cycloalkyl group (i.e. a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group), or a C_1-C_6 alkyl group (e.g. a methyl, ethyl, propyl, isopropyl, butyl,isobutyl, pentyl or hexyl group) optionally substituted by one, two, three or four substituents independently selected from amino, amido, hydroxyl, (di)C_1-C_4 alkylamino (e.g. (di)methylamino, (di)ethylamino, (di)propylamino or (di)butylamino), C_2-C_4 acylamino (e.g. acetylamino), C_1-C_4 alkoxy (e.g. methoxy, ethoxy, propoxy or butoxy) optionally substituted by one, two or three hydroxyls, and morpholinyl.

More preferably, R^3 and R^4 each independently represent a hydrogen atom, a cyclopropyl group, or a C_1-C_6 alkyl group optionally substituted by one or two substituents independently selected from amido, hydroxyl, dimethylamino, diethylamino, acetylamino, C_1-C_2 alkoxy optionally substituted by one hydroxyl, and morpholinyl.

It is preferred that R^2 represents a C_1-C_6 alkyl group (e.g. a methyl, ethyl, propyl, butyl, pentyl or hexyl group) or C_2-C_6 alkenyl group (e.g. an ethenyl, propenyl, butenyl, pentenyl

or hexenyl group), each of which may be optionally substituted by a phenyl or phenoxy group, the phenyl or phenoxy group being optionally substituted by one, two, three or four substituents independently selected from halogen atoms (e.g. fluorine, chlorine , bromine or iodine), nitro, trifluoromethyl, C_1-C_6 alkyl (e.g. methyl, ethyl, propyl, butyl, pentyl or hexyl), C_1-C_6 alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, pentoxy or hexoxy) and phenoxy.

It is further preferred that R^2 represents a C_1-C_6 alkyl group or C_2-C_4 alkenyl group, each of which may be optionally substituted by a phenyl or phenoxy group, the phenyl or phenoxy group being optionally substituted by one, two or three substituents independently selected from fluorine, chlorine, bromine, iodine, nitro, trifluoromethyl, C_1-C_4 alkyl (particularly methyl or ethyl), C_1-C_4 alkoxy (particularly methoxy) and phenoxy.

X represents a group -C(O)NH- or -C(NR^5R^6)=N- where R^5 and R^6 preferably each independently represent a hydrogen atom, a saturated hydrocarbyl ring system containing from 3 to 7 carbon atoms (e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or bicyclo[2.2.1]heptyl) optionally substituted by one, two or three hydroxyl groups, or a C_1-C_6 alkyl group (e.g. a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl or hexyl group) optionally substituted by one, two, three or four substituents independently selected from the group consisting of amino, hydroxyl, C_1-C_6 alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, pentoxy or hexoxy) optionally substituted by at least one hydroxyl (e.g. one, two or three hydroxyls), C_1-C_6 alkylthio (e.g. methylthio, ethylthio, propylthio, butylthio, pentylthio, hexylthio), (di)C_1-C_6 alkylamino (e.g. (di)methylamino, (di)ethylamino, (di)propylamino, (di)butylamino, (di)pentylamino or (di)hexylamino) optionally substituted by at least one hydroxyl (e.g. one, two or three hydroxyls), and phenyl optionally substituted by one, two, three or four substituents independently selected from halogen atoms (e.g. fluorine, chlorine, bromine or iodine), amino and hydroxyl; or R^5 and R^6 together with the nitrogen atom to which they are attached form a pyrrolidinyl or piperidinyl ring optionally substituted by one, two, three or four substituents independently

selected from hydroxyl, hydroxyC_1-C_6 alkyl (preferably hydroxyC_1-C_4 alkyl) and benzyloxycarbonyl.

More preferably, R^5 and R^6 each independently represent a hydrogen atom, a saturated hydrocarbyl ring system containing from 3 to 7 carbon atoms optionally substituted by one hydroxyl group, or a C_1-C_6 alkyl group optionally substituted by one or two substituents independently selected from the group consisting of amino, hydroxyl, C_1-C_4 alkoxy optionally substituted by one hydroxyl, C_1-C_4 alkylthio, C_1-C_4 alkylamino optionally substituted by one hydroxyl, and phenyl optionally substituted by one or two substituents independently selected from chlorine, amino and hydroxyl; or R^5 and R^6 together with the nitrogen atom to which they are attached form a pyrrolidinyl or piperidinyl ring optionally substituted by one or two substituents independently selected from hydroxyl, hydroxymethyl and benzyloxycarbonyl.

Particularly preferred compounds of the invention include:
(R)-2-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol,
(S)-2-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol,
2-Amino-5-(((2,3-difluorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
5-(((3-Phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
(±)-2-((2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol,
2-((2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7-yl)amino)ethanol,
5-(Pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Bromo-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-((3-(Dimethylamino)propyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-((2-(Diethylamino)ethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-((2-(Dimethylamino)ethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-((3-Hydroxypropyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-((2-(Acetylamino)ethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
(±)-2-((2,3-Dihydoxypropyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-((2-(4-Morpholinyl)ethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-((2-Methoxyethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-((1-Methylethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-(Cyclopropylamino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
(±)-2-((2-Hydoxypropyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-((2-(2-Hydroxyethoxy)ethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-((2-Hydroxy-2-methylpropyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-((2-Hydroxyethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
(2S,3R)-3-Hydroxy-2-((7-oxo-5-(pentylthio)-4H-thiazolo[4,5-d]pyrimidin-2-yl)-amino)butanamide,
N^7-(3-(Dimethylamino)propyl)-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine,
N^7-(2-(Diethylamino)ethyl)-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine,
N^7-(2-(Dimethylamino)ethyl)-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine,
3-((2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-propanol,
N^7-Cyclohexyl-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine,
(±)-3-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1,2-propanediol,
N^7-(2-Methoxyethyl)-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine,
5-(Pentylthio)-N^7-propylthiazolo[4,5-d]pyrimidine-2,7-diamine,
N^7-Cyclopentyl-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine,
N^7-Cyclopropyl-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine,
N^7-(2-Methylpropyl)-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine,
(±)-1-((2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2-propanol,
(exo)-N^7-Bicyclo[2.2.1]hept-2-yl-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine,
2-(2-((2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7-yl)amino)ethoxy)ethanol,
(±)-N^7-(2-Methylbutyl)-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine,
1-((2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2-methyl-2-propanol,
N^7-((2-Aminophenyl)methyl)-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine,

2-Amino-5-((2-phenoxyethyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
E-2-Amino-5-((3-phenyl-2-propenyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Amino-5-((3-(2,4-bis(1,1-dimethylethyl)phenoxy)propyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Amino-5-(((4-(trifluoromethyl)phenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Amino-5-(((3,5-dichlorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Amino-5-(((2,4-dichlorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Amino-5-(((3,4-dichlorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Amino-5-(((3,5-dibromophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Amino-5-(((2-nitrophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Amino-5-(((2-fluorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Amino-5-(((2-iodophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Amino-5-(((3-chlorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Amino-5-(((2-chlorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Amino-5-(((4-chloro-2-nitrophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Amino-5-(((3-chloro-4-methoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Amino-5-(((2,3-dichlorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Amino-5-(((3,5-difluorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Amino-5-(((2,4-bis(trifluoromethyl)phenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Amino-5-(((2-bromophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Amino-5-(((2,3,4-trifluorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Amino-5-(((3-bromophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
2-Amino-5-(((2-fluoro-3-methylphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,
3-(2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2,2-dimethyl-1-propanol,
(±)-α-(((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)methyl)benzenemethanol,
(R)-β-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)benzenepropanol,

2-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)ethanol,
(R)-2-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-4-methylpentanol,
(±)-1-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2-propanol,
(±)-β-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-4-chlorobenzenepropanol,
(±)-3-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1,2-propanediol,
2-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)propylamino)ethanol,
(±)-1-(2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-3-pyrrolidinol,
(±)-1-(2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-3-piperidinol,
1-(2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-4-piperidinol,
3-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2,2-dimethyl-1-propanol,
(±)-2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol,
(±)-α-(((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-amino)methyl)benzenemethanol,
4-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol,
6-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-hexanol,
4-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-amino)cyclohexanol,
(R)-β-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-amino)benzenepropanol,
(±)-2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-propanol,
2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-amino)ethanol,

(R)-2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-4-methylpentanol,

(±)-1-Amino-3-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2-propanol,

(±)-1-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2-propanol,

2-(((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)methyl)-2-ethyl-1,3-propanediol,

(±)-β-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-4-chlorobenzenepropanol,

(±)-3-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1,2-propanediol,

2-((2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)ethyl)amino)ethanol,

3-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-propanol,

(±)-α-(((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)methyl)-3,4-dichlorobenzenepropanol,

1-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2-methyl-2-propanol,

2-(2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)ethoxy)ethanol,

5-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-pentanol,

(S)-2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-4-(methylthio)-1-butanol,

2-((2-Amino-5-((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)butylamino)ethanol,

2-((2-Amino-5-((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)propylamino)ethanol,

2,2'-((2-Amino-5-((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)imino)bisethanol,

2-(((2-Amino-5-((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)(2-hydroxyethyl)amino)methyl)phenol,

3-((2-Amino-5-((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)(2-hydroxyethyl)amino)-1-propanol,

(±)-1-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-3-pyrrolidinol,

trans-1-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-4-hydroxy-L-proline phenylmethyl ester,

(±)-1-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-3-piperidinemethanol,

(±)-1-(2-Amino-5-((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-3-piperidinol,

(S)-1-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-2-pyrrolidinemethanol,

1-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-4-piperidinol,

(R)-2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol,

(S)-2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol,

(R)-2-((2-Amino-5-(((2,3-difluorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol,

2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1,3-propanediol,

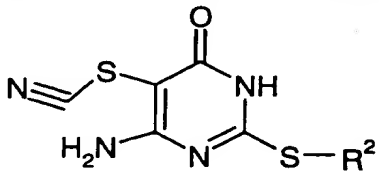
2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2-methyl-1-propanol,

2-((2-Amino-5-(((2,3-difluorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2-methyl-1-propanol,

and their pharmaceutically acceptable salts and solvates.

According to the invention there is also provided a process for the preparation of a compound of formula (I) which comprises:

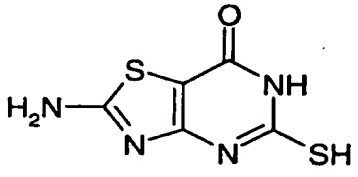
(a) when X represents -C(O)NH- and R^1 is NH_2, heating a compound of general formula



(II)

wherein R^2 is as defined in formula (I); or

(b) when X represents -C(O)NH- and R^1 is NH_2, reacting a compound of general formula



(III)

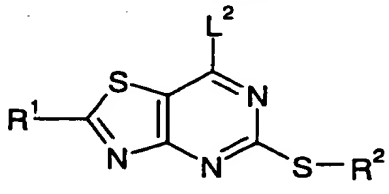
with a compound of general formula (IV), R^2 - L^1, wherein L^1 represents a leaving group such as a halogen atom (e.g. chlorine) and R^2 is as defined in formula (I); or

(c) when X represents -C(O)NH- and R^1 is a hydrogen atom, reacting a corresponding compound of formula (I) in which R^1 is NH_2, with a diazotizing agent; or

(d) when X represents -C(O)NH- and R^1 is a halogen atom, reacting a corresponding compound of formula (I) in which R^1 is NH_2, with a diazotizing agent and a halogenating agent; or

(e) when X represents -C(O)NH- and R^1 is a group $-NR^3R^4$, reacting a corresponding compound of formula (I) in which R^1 is a halogen atom, with a compound of general formula (V), R^3R^4NH, wherein R^3 and R^4 are as defined in formula (I); or

(f) when X represents $-C(NR^5R^6)=N-$, reacting a compound of general formula



(VI)

wherein L^2 represents a leaving group such as a halogen atom (e.g. chlorine) and R^1 and R^2 are as defined in formula (I), with a compound of general formula (VII), R^5R^6NH, wherein R^5 and R^6 are as defined in formula (I);

and optionally after (a), (b), (c), (d), (e) or (f) forming a pharmaceutically acceptable salt or solvate of the compound of formula (I).

Process (a) is conveniently carried out in the presence of a solvent or solvent mixture such as dimethylformamide/water at a temperature in the range from e.g. 50 to 150°C.

Process (b) is conveniently carried out in an organic solvent such as tetrahydrofuran or dimethyl sulphoxide/dimethylformamide mixture, optionally in the presence of a base such as potassium *tert*-butoxide or diisopropylamide.

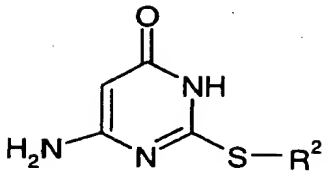
Process (c) is conveniently carried out in an organic solvent such as tetrahydrofuran. Examples of suitable diazotizing agents to use include *tert*-butyl nitrite.

Process (d) is conveniently carried out in an organic solvent such as acetonitrile in the presence of a diazotizing agent such as *tert*-butyl nitrite and a halogenating agent such as a trimethylsilyl halide.

Process (e) is conveniently carried out in an organic solvent such as tetrahydrofuran, e.g. at a temperature of 50°C for 5 hours.

Process (f) is conveniently carried out in an organic solvent such as tetrahydrofuran with heating for a period in the range from 1 day to 3 weeks.

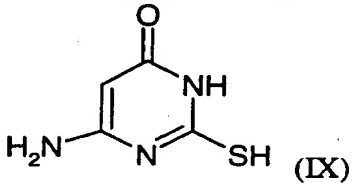
Compounds of formula (II) may be readily prepared by reacting a compound of general formula



(VIII)

wherein R^2 is as defined above, with potassium thiocyanate in dimethylformamide, followed by reaction with bromine in pyridine.

Compounds of formula (VIII) are suitably prepared by reacting a compound of formula



(IX)

with a compound of formula (IV) as defined above.

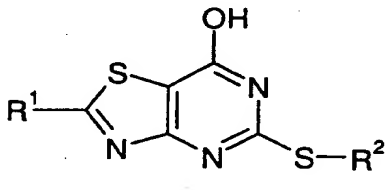
Compounds of formula (VI) in which L^2 is a chlorine atom may be prepared by reacting a compound of formula (I) in which X is -C(O)NH- with phosphorus oxychloride in dimethylaniline under reflux conditions.

Compounds of formulae (III), (IV), (V), (VII) and (IX) are either commercially available, are well known in the literature or may be prepared easily using known techniques.

It will be appreciated by those skilled in the art that in the processes described above the functional groups (e.g. hydroxyl or amino groups) of intermediate compounds may need to be protected by protecting groups. The final stage in the preparation of the compounds of the invention may involve the removal of one or more protecting groups. The protection and deprotection of functional groups is fully described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T. W. Greene & P. G. M. Wuts, Wiley–Interscience (1991).

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

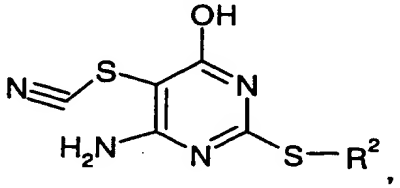
Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention, particularly tautomers of general formula



(I')

wherein R^1 and R^2 are as defined in formula (I).

Similarly, it will be understood that in the above processes tautomeric forms of the compounds of formulae (II), (III), (VIII) and (IX) may also be used, e.g.



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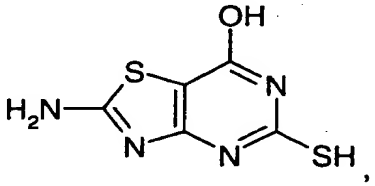

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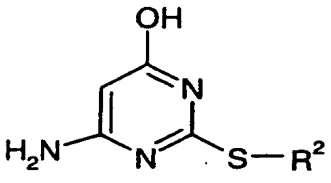

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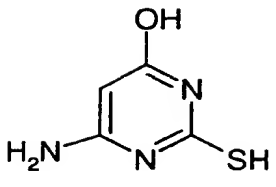
and



The compounds of formula (I) may be used in the treatment (therapeutic or prophylactic) of conditions/diseases (particularly inflammatory diseases) in human and non-human animals which are exacerbated or caused by excessive or unregulated production of chemokines that bind to the IL-8α (CXCR1) or IL-8β (CXCR2) receptor by acting as antagonists of the IL-8α or β receptor. Examples of such conditions include:

(1) **(the respiratory tract)** reversible obstructive airways diseases including asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;

(2) **(bone and joints)** rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

(3) **(skin)** psoriasis, atopical dermatitis, contact dermatitis and other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus,

Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis;

(4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

(5) **(other tissues and systemic disease)** multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, sezary syndrome and idiopathic thrombocytopenia pupura;

(6) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;

(7) cancers, especially non-small cell lung cancer (NSCLC) and squamous sarcoma; and

(8) diseases in which angiogenesis is associated with raised CXCR2 chemokine levels (e.g. NSCLC).

Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention still further provides a method of treating a chemokine mediated disease wherein the chemokine binds to an IL-8α or β receptor, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

The invention also provides a method of treating an inflammatory disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

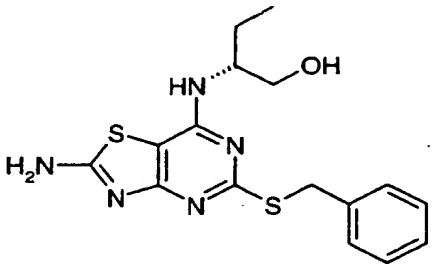
The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally.

The invention will now be further illustrated by reference to the following examples. In the examples the Nuclear Magnetic Resonance (NMR) spectra were measured on a Varian Unity Inova 300 or 400 MHz spectrometer and the Mass Spectrometry (MS) spectra measured on a Finnigan Mat SSQ7000 or Micromass Platform spectrometer. Where necessary, the reactions were performed under an inert atmosphere of either nitrogen or argon. Chromatography was generally performed using Matrex Silica 60® (35-70 micron) or Prolabo Silica gel 60® (35-70 micron) suitable for flash silica gel chromatography. The abbreviations m.p. and DMSO used in the examples stand for melting point and dimethyl sulphoxide respectively.

Example 1

(R)-2-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol



(a) **7-Chloro-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-2-amine**

2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one (0.89g), phosphorus oxychloride (12mL) and N,N-dimethylaniline (1.2mL) were heated at reflux for 2 hours. The cooled reaction mixture was poured onto ice and water and stirred for 2 hours. Chromatography on silica eluting with methanol/dichloromethane mixtures gave the sub-title chloride.

m.p. 217-218.5°C

MS: APCI(+ve) 309/11 (M+1)

^{1}H NMR: δ (DMSO) 4.38 (s,2H), 7.20-7.48 (m,5H) and 8.95 (br s,2H).

(b) (R)-2-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol

The chloro compound from step (a) (0.12g) in tetrahydrofuran (3 mL) was treated with (R)-2-amino-1-butanol (0.56g) and the reaction mixture was heated at reflux for 5 days. Dichloromethane and dilute hydrochloric acid were added. The resulting solid was filtered off, washed with water and ether to give the title compound which was obtained containing 0.23 moles of hydrogen chloride and 0.93 moles of water. Yield 0.045g.

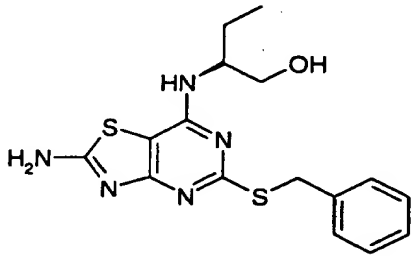
m.p. 118-121°C

MS: APCI(+ve) 362 (M+1)

^{1}H NMR: δ (DMSO) 0.83 (t,3H), 1.45 (m,2H), 1.65 (m,2H), 3.39 (m,2H), 4.31 (q,2H), 4.65 (t,1H), 6.91 (d,1H), 7.17-7.44 (m,5H) and 8.00 (s,2H).

Example 2

(S)-2-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol



Prepared by the method of Example 1(b) from the chloro compound of Example 1(a) and (S)-2-amino-1-butanol. Obtained as a solid containing 0.7 moles of hydrogen chloride.

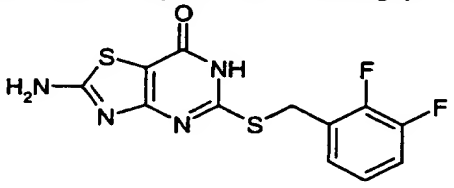
mp 204-208°C

MS: APCI(+ve) 362 (M+1)

^{1}H NMR: δ (DMSO) 0.82 (t,3H), 1.37-1.74 (m,2H), 3.36-3.52 (m,2H), 4.10 (br s,1H), 4.41 (q,2H), 7.20-7.46 (m,5H), 7.63 (br s,1H) and 8.42 (s,2H).

Example 3

2-Amino-5-(((2,3-difluorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



Potassium t-butoxide solution (0.45mL of 1M in tetrahydrofuran) was added to a stirred solution of 2-amino-5,6-dihydro-5-thioxothiazolo[4,5-d]pyrimidin-7(4H)-one (0.09g) and 2,3-difluorobenzyl bromide in dimethyl sulphoxide (2mL). After stirring for 3 days, the reaction mixture was poured onto water. The title compound was obtained. Yield 0.065g.

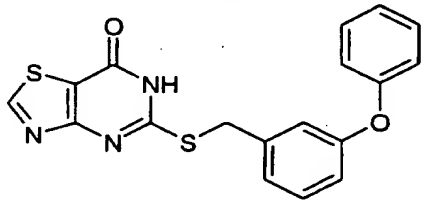
m.p. 310-313°C

MS: APCI(+ve) 327 (M+1)

^{1}H NMR: δ (DMSO) 4.48 (s,2H), 7.18-7.45 (m,3H), 8.20 (s,2H) and 12.62 (s,1H).

Example 4

5-(((3-Phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one (0.3g) was added over 90 minutes to a solution of t-butyl nitrite (0.17mL) in tetrahydrofuran (3mL) at 65°C. After a further 3.5 hours at 65°C, the solvent was evaporated and the residue chromatographed on silica eluting with methanol/dichloromethane mixtures to give the title compound. Yield 0.071g.

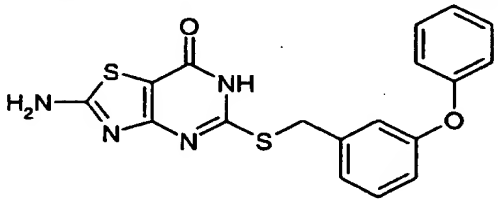
m.p. 197-198°C

MS: APCI(+ve) 368 (M+1)

^{1}H NMR: δ (DMSO) 4.49 (s,2H), 6.86-7.38 (m,9H), 9.58 (s,1H) and 13.11 (s,1H).

Example 5

2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



Prepared by the method of Example 3 using 3-phenoxybenzyl chloride.

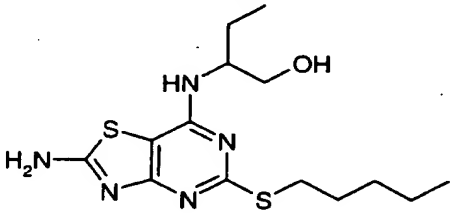
m.p. 266-269°C

MS: APCI(+ve) 383 (M+1)

^{1}H NMR: δ (DMSO) 4.40 (s,2H), 6.81-7.41 (m,9H), 8.15 (s,2H) and 12.55 (s,1H).

Example 6

(±)-2-((2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol



(a) 7-Chloro-5-(pentylthio)thiazolo[4,5-d]pyrimidin-2-amine

Prepared by the method of Example 1(a) from 2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one.

m.p. 176.5-177.5°C

MS: APCI(+ve) 289 (M+1)

^{1}H NMR: δ (DMSO) 0.88 (t,3H), 1.22-1.42 (m,4H), 1.60-1.74 (m,2H), 3.08 (t,2H) and 8.90 (s,2H).

(b) (±)-2-((2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol

Prepared by the method of Example 1(b) from the chloro compound of Example 6(a) and the appropriate amine.

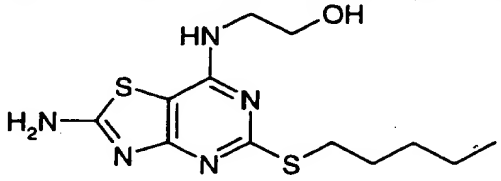
m.p. 151-154°C

MS: APCI(+ve) 342 (M+1)

^{1}H NMR: δ (DMSO) 0.82-0.95 (m,6H), 1.22-1.72 (m,8H), 3.04 (m,2H), 3.39-3.56 (m,2H), 4.07 (m,1H), 4.64 (t,1H), 6 88 (d,1H), 7.44 (br s,1H) and 7.96 (s,2H).

Example 7

2-((2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7-yl)amino)ethanol



Prepared by the method of Example 6(b).

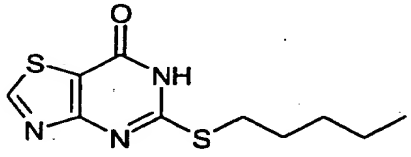
m.p. 192-195°C

MS: APCI(+ve) 314 (M+1)

^{1}H NMR: δ (DMSO) 0.87 (t,3H), 1.21-1.42 (m,4H), 1.57-1.70 (m,2H), 2.99 (t,2H), 3.37-3.46 (m,2H), 3.46-3.58 (m,2H), 4.71 (t,1H), 7.22 (t,1H) and 7.97 (s,2H).

Example 8

5-(Pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one



Prepared by the method of Example 4.

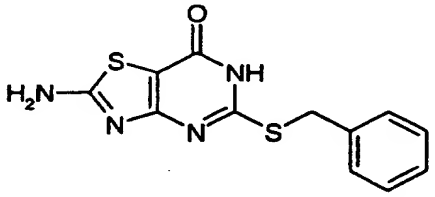
m.p. 208-209°C

MS: APCI(+ve) 256 (M+1)

^{1}H NMR: δ (DMSO) 0.88 (t,3H), 1.22-1.44 (m,4H), 1.63-1.75 (m,2H), 3.20 (t,2H), 9.57 (s,1H) and 13.06 (s,1H).

Example 9

2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



(a) 6-Amino-2-((phenylmethyl)thio)-5-thiocyanato-4(1H)-pyrimidinone

6-Amino-2-((phenylmethyl)thio)-4(1H)-pyrimidinone (10.5g) and potassium thiocyanate (25g) in dimethylformamide (200mL) were heated together at 65°C. Pyridine (6.3mL) was added and the solution cooled to 5°C. Bromine (2.2mL) was added slowly and the reaction mixture stirred for 2 hours at 5-10°C. The reaction mixture was poured onto ice and water, stirred for 1 hour and the solid was filtered off. After washing with water and ether a pure sample was obtained after tituration with hot methanol.

m.p. 260-262°C

MS: APCI(+ve) 291 (M+1)

^{1}H NMR: δ (DMSO) 4.38 (s,2H), 7.21-7.51 (m,5H), 7.70 (br s,2H) and 12.35 (s,1H).

(b) 2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one

The product of step (a) (7.35g) was heated at 120°C in dimethylformamide (40mL) and water (10mL) for 10 hours. After cooling, the resulting solid was filtered off, washed with water, ether and ethyl acetate to give the title compound containing 0.4 moles of dimethylformamide.

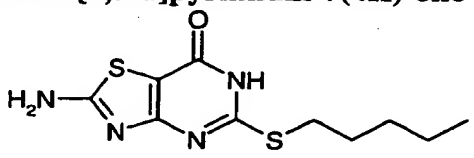
m.p. ~325°

MS: APCI(+ve) 291 (M+1)

^{1}H NMR: δ (DMSO) 4.41 (s,2H), 7.21-7.50 (m,5H), 8.17 (s,2H) and 12.53 (br s,1H).

Example 10

2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one



(a) 6-Amino-2-(pentylthio)-5-thiocyanato-4(1H)-pyrimidinone

Prepared by the method of Example 9(a).

m.p. 260-262°C

MS: APCI(+ve) 214 (M+1)

^{1}H NMR: δ (DMSO) 0.86 (t,3H), 1.22-1.40 (m,4H), 1.56-1.68 (m,2H), 3.10 (t,2H), 7.58 (br s,2H) and 12.30 (s,1H).

(b) 2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one

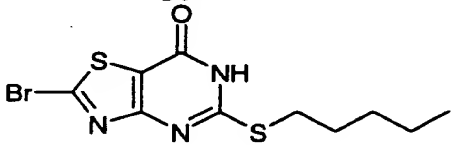
Prepared by the method of Example 9(b).

MS: APCI(+ve) 271 (M+1)

^{1}H NMR: δ (DMSO) 0.86 (t,3H), 1.24-1.40 (m,4H), 1.58-1.70 (m,2H), 3.12 (t,2H), 8.12 (br s,2H) and 12.49 (s,1H).

Example 11

2-Bromo-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one



Trimethylsilyl bromide (0.44mL) was added slowly to a solution at 0°C under nitrogen of t-butyl nitrite (0.42mL) in acetonitrile (2mL). After 30 minute at 0°C, 2-amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one (0.5g) was added. The reaction mixture was stirred at room temperature for 16 hours and the solvent was evaporated. Chromatography on silica eluting with dichloromethane/methanol mixtures gave the title bromide.

m.p. 189-191°C

MS: APCI(+ve) 336/7 (M+1)

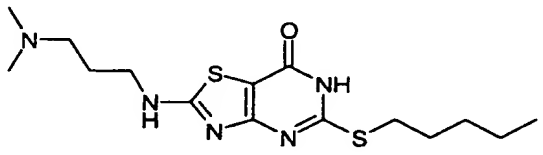
^{1}H NMR: δ (DMSO) 0.88 (t,3H), 1.26-1.41 (m,4H), 1.64-1.75 (m,2H), 3.18 (t,2H) and 13.22 (s,1H).

Examples 12-26

The compounds of Examples 12 to 26 were prepared by heating 2-bromo-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one with 5 equivalents of the appropriate amine in tetrahydrofuran at 45°C for 5 hours.

Example 12

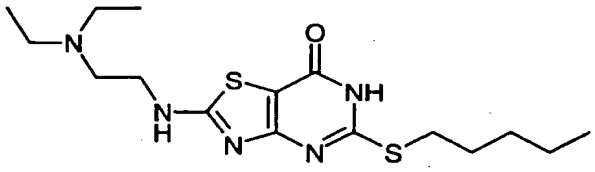
2-((3-(Dimethylamino)propyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 356 (M+1)

Example 13

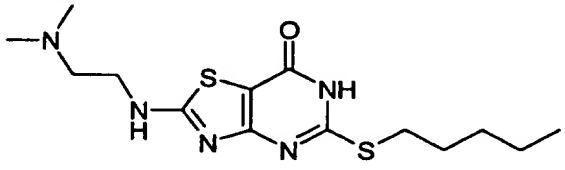
2-((2-(Diethylamino)ethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 370 (M+1)

Example 14

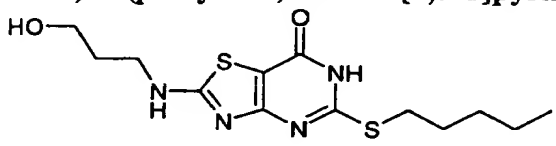
2-((2-(Dimethylamino)ethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 342 (M+1)

Example 15

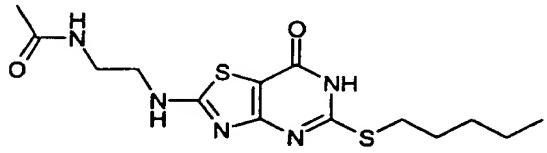
2-((3-Hydroxypropyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 329 (M+1)

Example 16

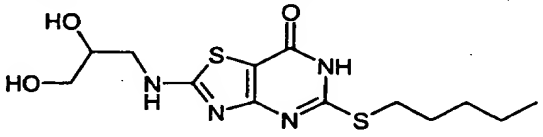
2-((2-(Acetylamino)ethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 356 (M+1)

Example 17

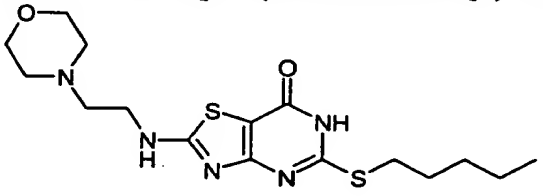
(±)-2-((2,3-Dihydoxypropyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 345 (M+1)

Example 18

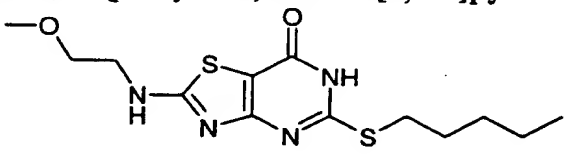
2-((2-(4-Morpholinyl)ethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 384 (M+1)

Example 19

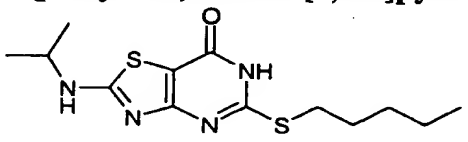
2-((2-Methoxyethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 329 (M+1)

Example 20

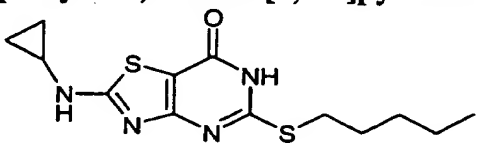
2-((1-Methylethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 313 (M+1)

Example 21

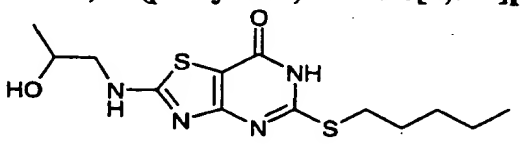
2-(Cyclopropylamino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 311 (M+1)

Example 22

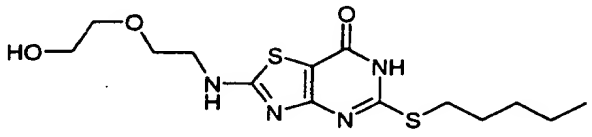
(±)-2-((2-Hydoxypropyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 329 (M+1)

Example 23

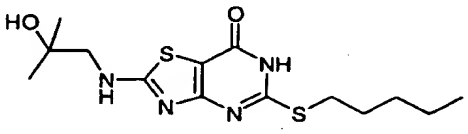
2-((2-(2-Hydroxyethoxy)ethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 359 (M+1)

Example 24

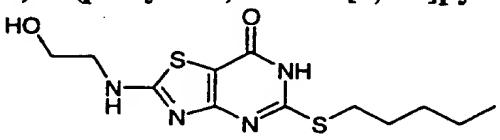
2-((2-Hydroxy-2-methylpropyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 343 (M+1)

Example 25

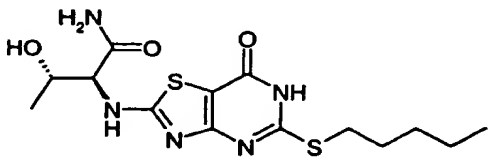
2-((2-Hydroxyethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 315 (M+1)

Example 26

(2S,3R)-3-Hydroxy-2-((7-oxo-5-(pentylthio)-4H-thiazolo[4,5-d]pyrimidin-2-yl)-amino)butanamide



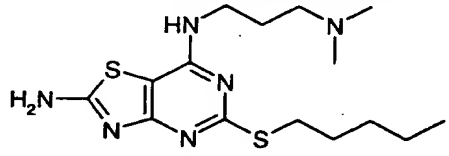
MS: APCI (+ve) 372 (M+1)

Examples 27-43

The compounds of Examples 27 to 43 were prepared by heating 7-chloro-5-(pentylthio)thiazolo[4,5-d]pyrimidin-2-amine with 5 equivalents of the appropriate amine in tetrahydrofuran at 45°C for 5 hours.

Example 27

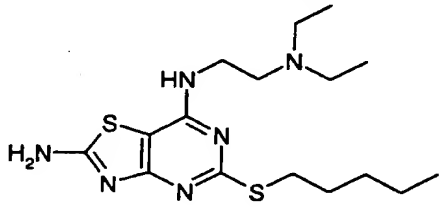
N^7-(3-(Dimethylamino)propyl)-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine



MS: APCI (+ve) 355 (M+1)

Example 28

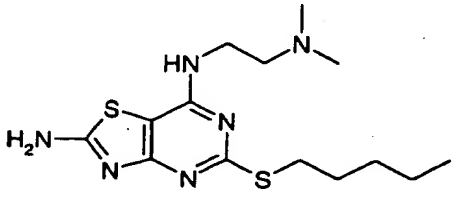
N^7-(2-(Diethylamino)ethyl)-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine



MS: APCI (+ve) 369 (M+1)

Example 29

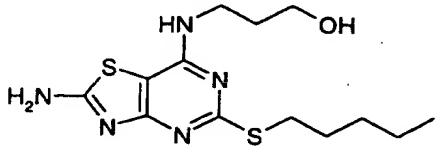
N^7-(2-(Dimethylamino)ethyl)-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine



MS: APCI (+ve) 341 (M+1)

Example 30

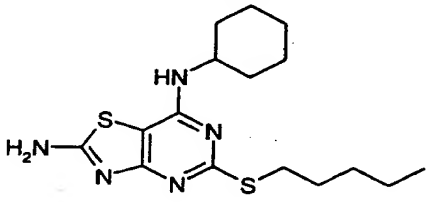
3-((2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-propanol



MS: APCI (+ve) 328 (M+1)

Example 31

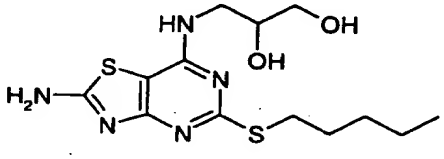
N^7-Cyclohexyl-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine



MS: APCI (+ve) 352 (M+1)

Example 32

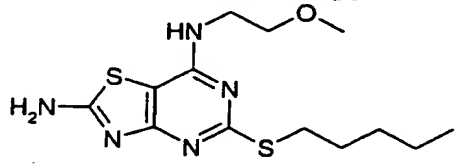
(±)-3-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1,2-propanediol



MS: APCI (+ve) 344 (M+1)

Example 33

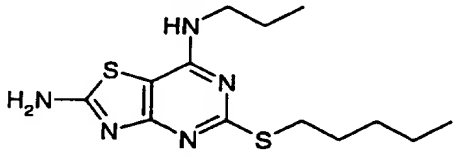
N^7-(2-Methoxyethyl)-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine



MS: APCI (+ve) 328 (M+1)

Example 34

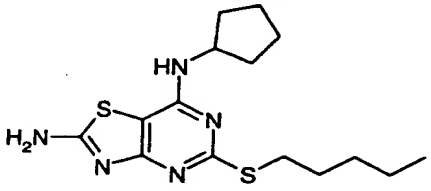
5-(Pentylthio)-N^7-propylthiazolo[4,5-d]pyrimidine-2,7-diamine



MS: APCI (+ve) 312 (M+1)

Example 35

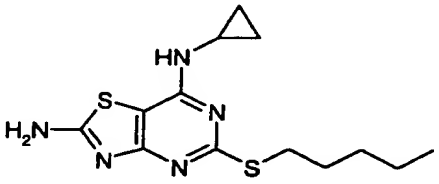
N^7-Cyclopentyl-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine



MS: APCI (+ve) 338 (M+1)

Example 36

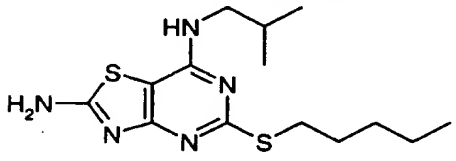
N^7-Cyclopropyl-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine



MS: APCI (+ve) 310 (M+1)

Example 37

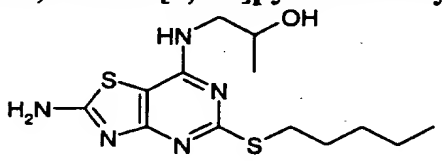
N^7-(2-Methylpropyl)-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine



MS: APCI (+ve) 326 (M+1)

Example 38

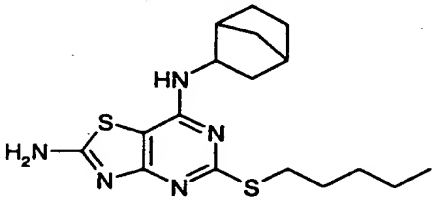
(±)-1-((2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2-propanol



MS: APCI (+ve) 328 (M+1)

Example 39

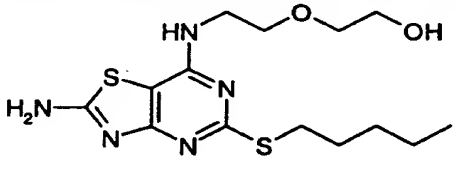
(exo)-N^7-Bicyclo[2.2.1]hept-2-yl-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine



MS: APCI (+ve) 364 (M+1)

Example 40

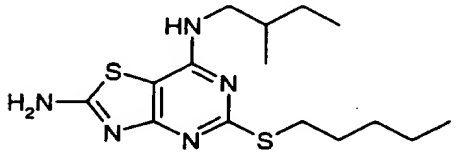
2-(2-((2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7-yl)amino)ethoxy)ethanol



MS: APCI (+ve) 358 (M+1)

Example 41

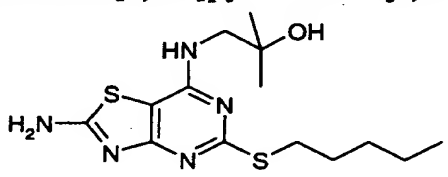
(±)-N^7-(2-Methylbutyl)-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine



MS: APCI (+ve) 340 (M+1)

Example 42

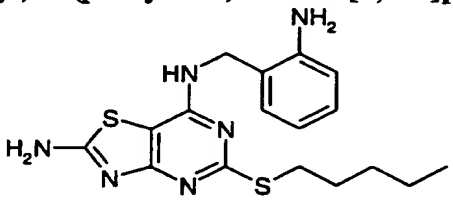
1-((2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2-methyl-2-propanol



MS: APCI (+ve) 342 (M+1)

Example 43

N^7-((2-Aminophenyl)methyl)-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine



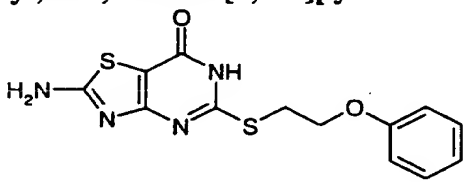
MS: APCI (+ve) 375 (M+1)

Examples 44-47

The compounds of Examples 44 to 47 were prepared from 2-amino-5,6-dihydro-5-thioxothiazolo[4,5-d]pyrimidin-7(4H)-one, diisopropylethylamine and the appropriate alkyl halide in dimethyl sulphoxide/dimethylformamide at 60°C. A total of 5 equivalents of base and alkyl halide were added over 3 days.

Example 44

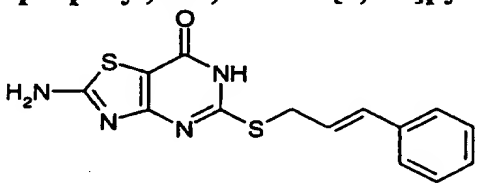
2-Amino-5-((2-phenoxyethyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 321 (M+1)

Example 45

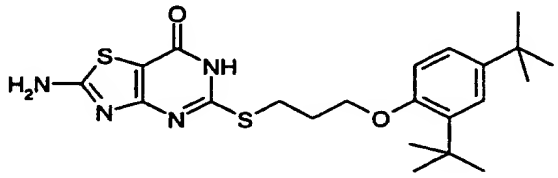
E-2-Amino-5-((3-phenyl-2-propenyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 317 (M+1)

Example 46

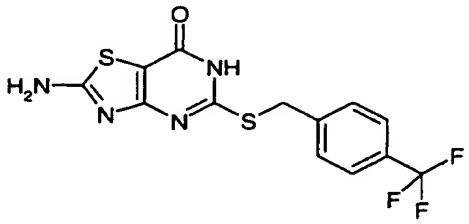
2-Amino-5-((3-(2,4-bis(1,1-dimethylethyl)phenoxy)propyl)thio)thiazolo[4,5-d]-pyrimidin-7(4H)-one



MS: APCI (+ve) 447 (M+1)

Example 47

2-Amino-5-(((4-(trifluoromethyl)phenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



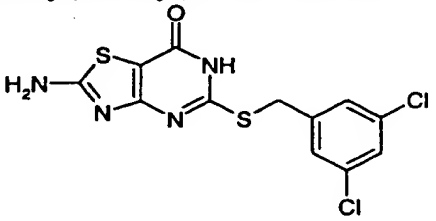
MS: APCI (+ve) 359 (M+1)

Examples 48-65

The compounds of Examples 48 to 65 were prepared from 2-amino-5,6-dihydro-5-thioxothiazolo[4,5-d]pyrimidin-7(4H)-one, potassium t-butoxide and the appropriate benzyl halide in dimethyl sulphoxide at room temperature. A total of 1.2 equivalents of base and alkyl halide were used and a reaction time of 24 hours.

Example 48

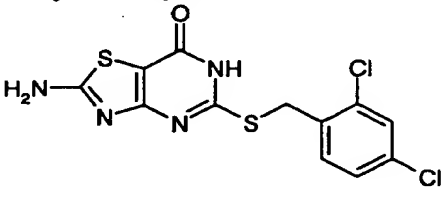
2-Amino-5-(((3,5-dichlorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 359 (M+1)

Example 49

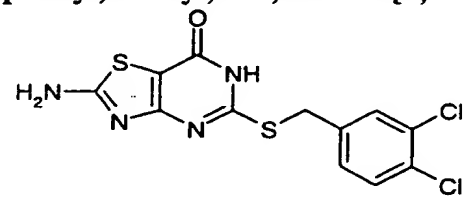
2-Amino-5-(((2,4-dichlorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 359 (M+1)

Example 50

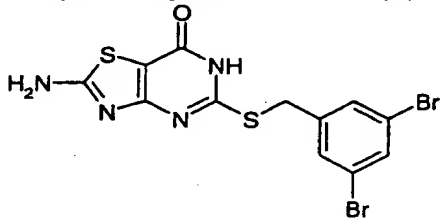
2-Amino-5-(((3,4-dichlorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 359 (M+1)

Example 51

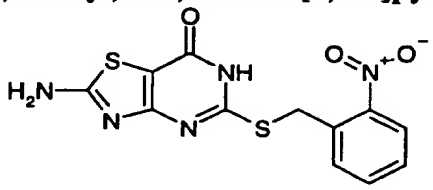
2-Amino-5-(((3,5-dibromophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 449 (M+1)

Example 52

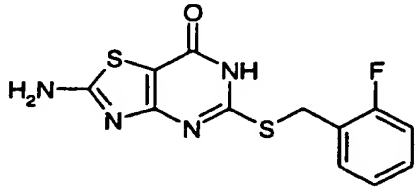
2-Amino-5-(((2-nitrophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 336 (M+1)

Example 53

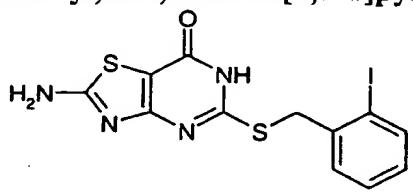
2-Amino-5-(((2-fluorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 309 (M+1)

Example 54

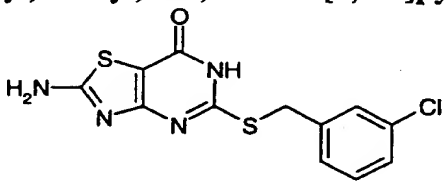
2-Amino-5-(((2-iodophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 417 (M+1)

Example 55

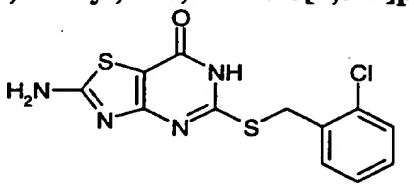
2-Amino-5-(((3-chlorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 325 (M+1)

Example 56

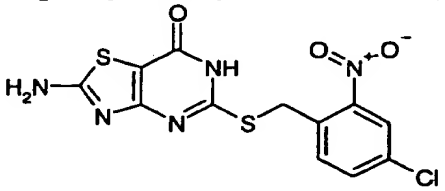
2-Amino-5-(((2-chlorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 325 (M+1)

Example 57

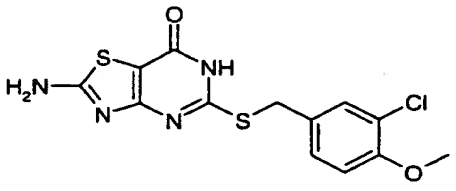
2-Amino-5-(((4-chloro-2-nitrophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 370 (M+1)

Example 58

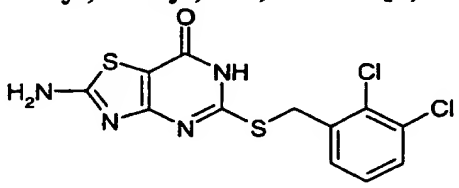
2-Amino-5-(((3-chloro-4-methoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 355 (M+1)

Example 59

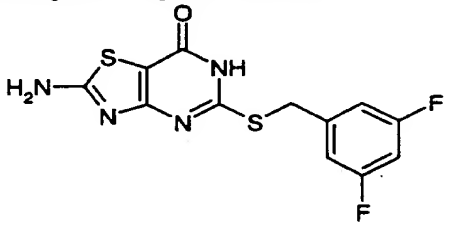
2-Amino-5-(((2,3-dichlorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 359 (M+1)

Example 60

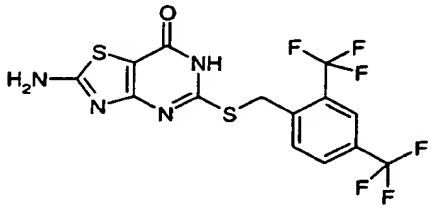
2-Amino-5-(((3,5-difluorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 327 (M+1)

Example 61

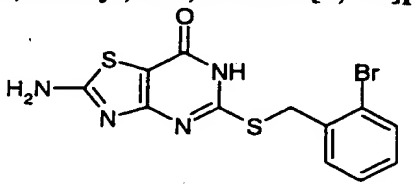
2-Amino-5-(((2,4-bis(trifluoromethyl)phenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 427 (M+1)

Example 62

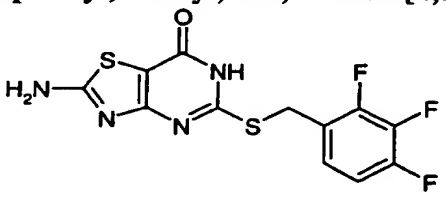
2-Amino-5-(((2-bromophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 371 (M+1)

Example 63

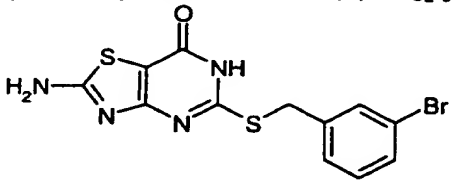
2-Amino-5-(((2,3,4-trifluorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 345 (M+1)

Example 64

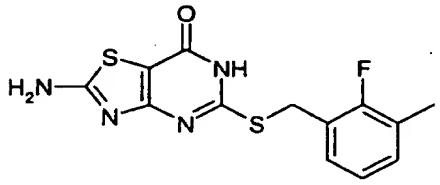
2-Amino-5-(((3-bromophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



MS: APCI (+ve) 369 (M+1)

Example 65

2-Amino-5-(((2-fluoro-3-methylphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one



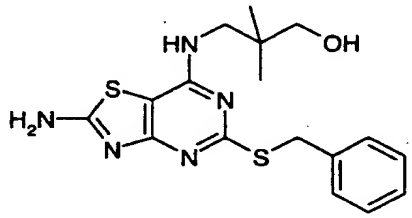
MS: APCI (+ve) 323 (M+1)

Examples 66-77

The compounds of Examples 66 to 77 were prepared from 7-chloro-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-2-amine and the appropriate hydroxyamine in dimethyl sulphoxide at 45°C. A total of 6 equivalents of amine were added and the reaction time was 2 days.

Example 66

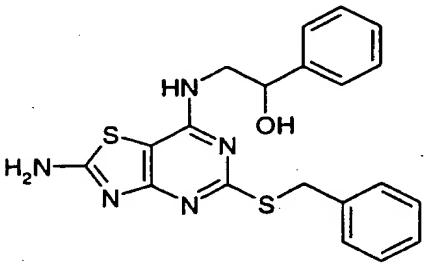
3-(2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2,2-dimethyl-1-propanol



MS: APCI (+ve) 376 (M+1)

Example 67

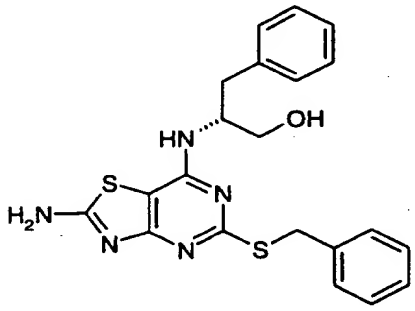
(±)-α-(((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)methyl)benzenemethanol



MS: APCI (+ve) 410 (M+1)

Example 68

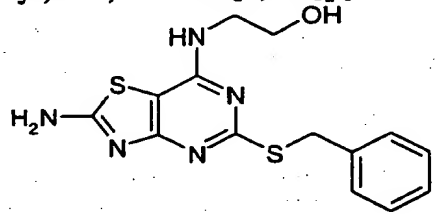
(R)-β-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)benzenepropanol



MS: APCI (+ve) 424 (M+1)

Example 69

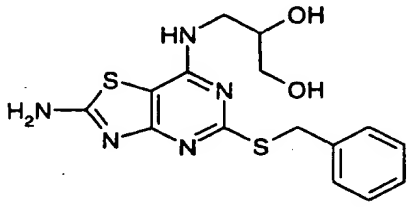
2-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)ethanol



MS: APCI (+ve) 334 (M+1)

Example 73

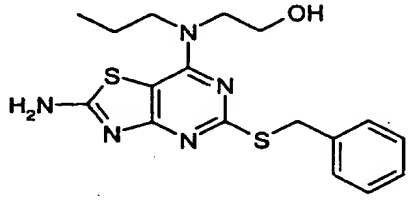
(±)-3-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1,2-propanediol



MS: APCI (+ve) 364 (M+1)

Example 74

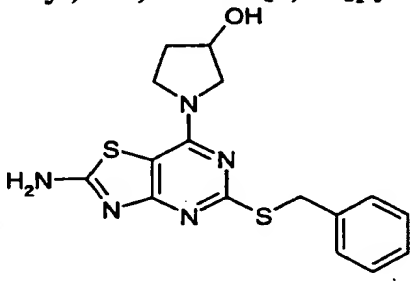
2-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-propylamino)ethanol



MS: APCI (+ve) 376 (M+1)

Example 75

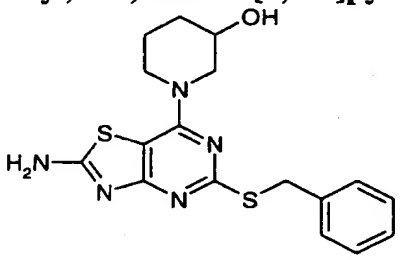
(±)-1-(2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-3-pyrrolidinol



MS: APCI (+ve) 360 (M+1)

Example 76

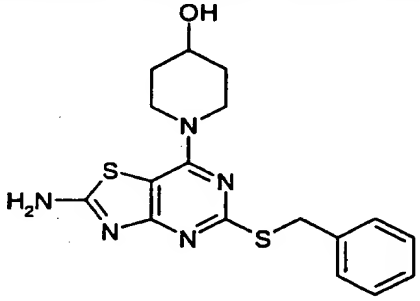
(±)-1-(2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-3-piperidinol



MS: APCI (+ve) 374 (M+1)

Example 77

1-(2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-4-piperidinol



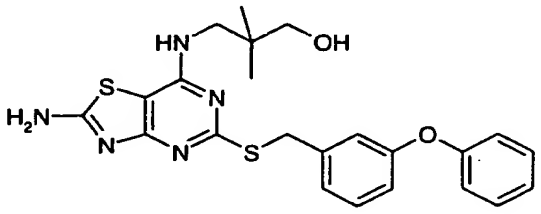
MS: APCI (+ve) 374 (M+1)

Examples 78-110

The compounds of Examples 78 to 110 were prepared from 7-chloro-5-((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-2-amine and the appropriate hydroxyamine in tetrahydrofuran at 45°C. A total of 6 equivalents of amine were added and the reaction time was 2 days.

Example 78

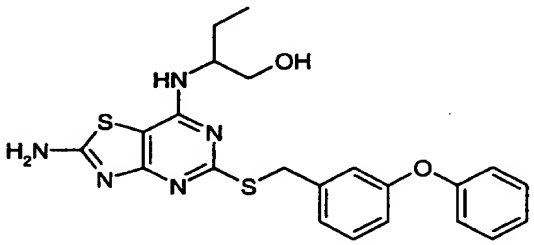
3-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2;2-dimethyl-1-propanol



MS: APCI (+ve) 468 (M+1)

Example 79

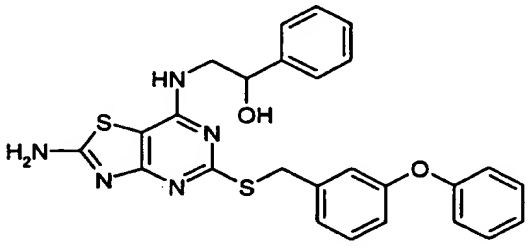
(±)-2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-amino)-1-butanol



MS: APCI (+ve) 454 (M+1)

Example 80

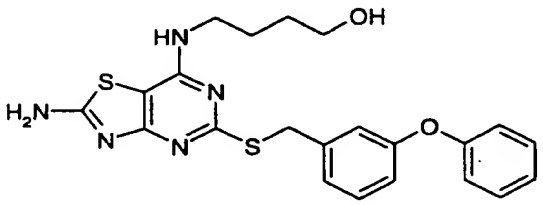
(±)-α-(((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-amino)methyl)benzenemethanol



MS: APCI (+ve) 502 (M+1)

Example 81

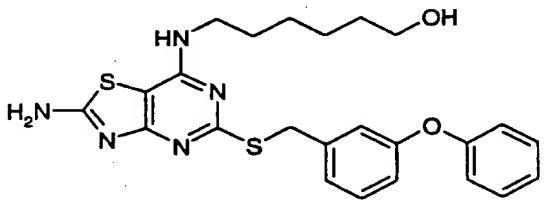
4-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol



MS: APCI (+ve) 454 (M+1)

Example 82

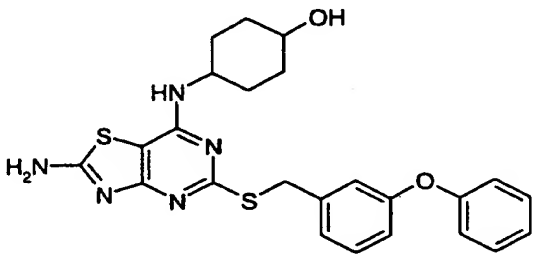
6-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-hexanol



MS: APCI (+ve) 482 (M+1)

Example 83

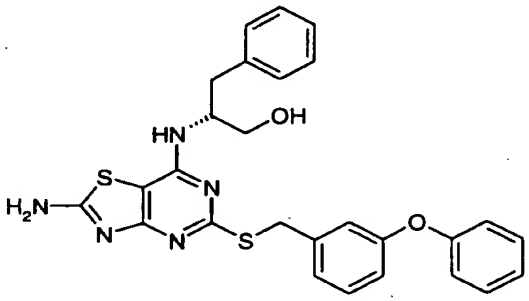
4-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-amino)cyclohexanol



MS: APCI (+ve) 480 (M+1)

Example 84

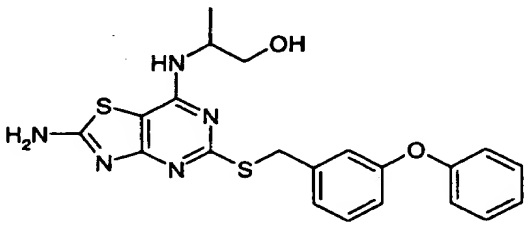
(R)-β-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-amino)benzenepropanol



MS: APCI (+ve) 516 (M+1)

Example 85

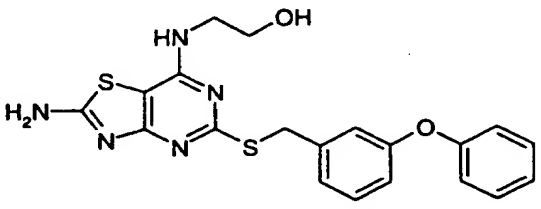
(±)-2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-amino)-1-propanol



MS: APCI (+ve) 440 (M+1)

Example 86

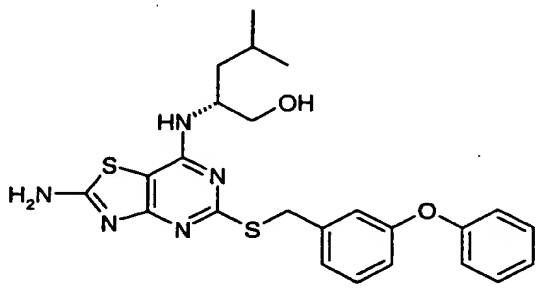
2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-amino)ethanol



MS: APCI (+ve) 426 (M+1)

Example 87

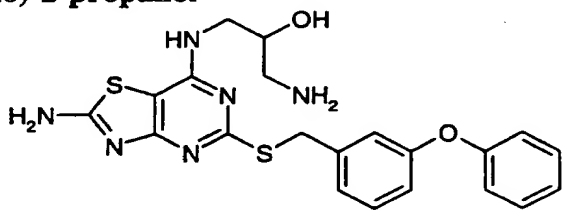
(R)-2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-amino)-4-methylpentanol



MS: APCI (+ve) 482 (M+1)

Example 88

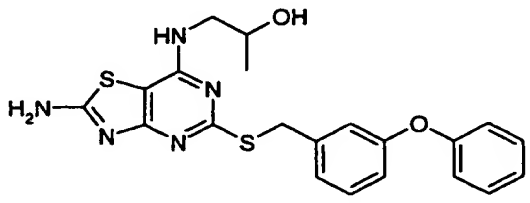
(±)-1-Amino-3-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2-propanol



MS: APCI (+ve) 455 (M+1)

Example 89

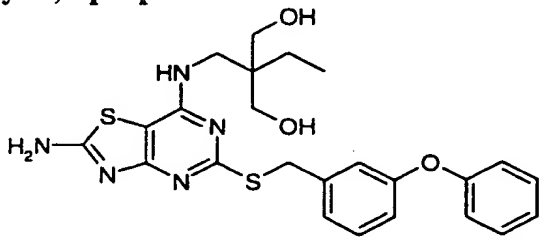
(±)-1-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2-propanol



MS: APCI (+ve) 440 (M+1)

Example 90

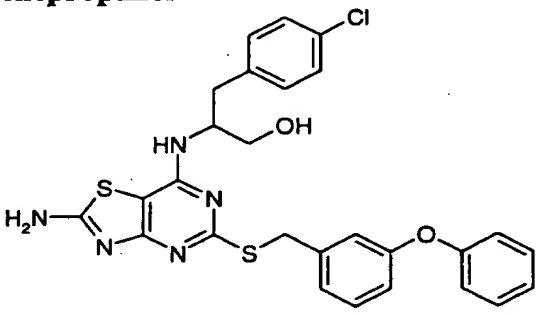
2-(((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)methyl)-2-ethyl-1,3-propanediol



MS: APCI (+ve) 498 (M+1)

Example 91

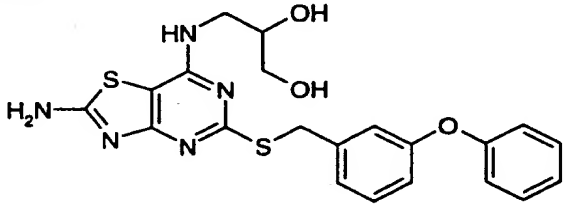
(±)-β-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-4-chlorobenzenepropanol



MS: APCI (+ve) 550 (M+1)

Example 92

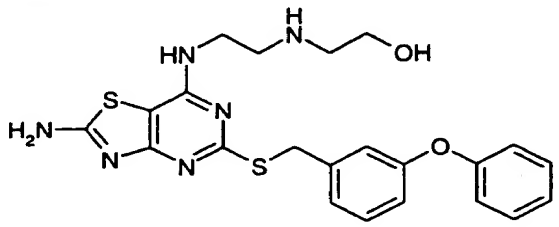
(±)-3-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1,2-propanediol



MS: APCI (+ve) 456 (M+1)

Example 93

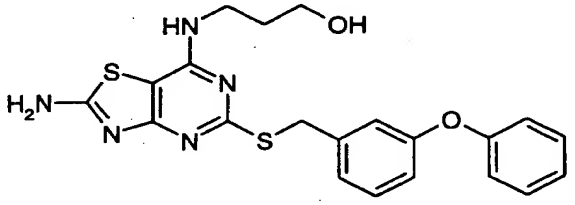
2-((2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)ethyl)amino)ethanol



MS: APCI (+ve) 469 (M+1)

Example 94

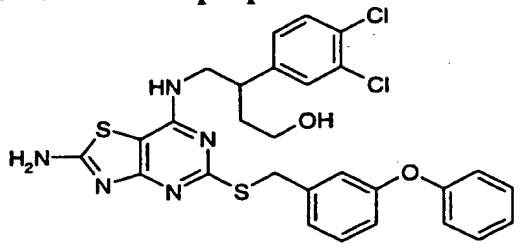
3-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-propanol



MS: APCI (+ve) 440 (M+1)

Example 95

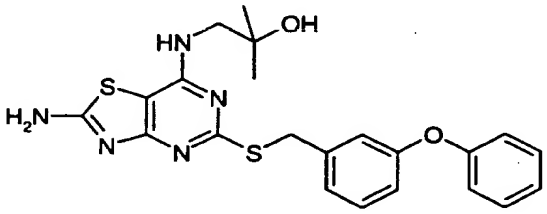
(±)-α-(((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)methyl)-3,4-dichlorobenzenepropanol



MS: APCI (+ve) 598 (M+1)

Example 96

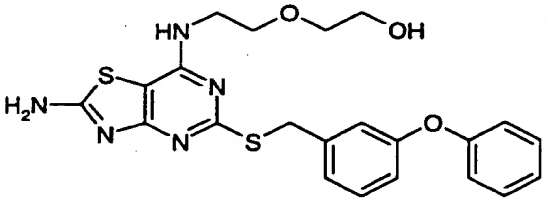
1-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2-methyl-2-propanol



MS: APCI (+ve) 454 (M+1)

Example 97

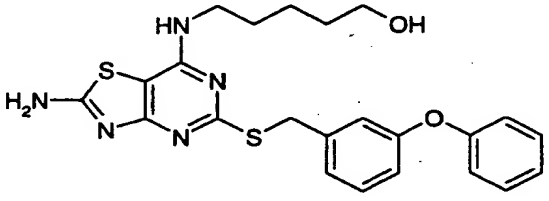
2-(2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)ethoxy)ethanol



MS: APCI (+ve) 470 (M+1)

Example 98

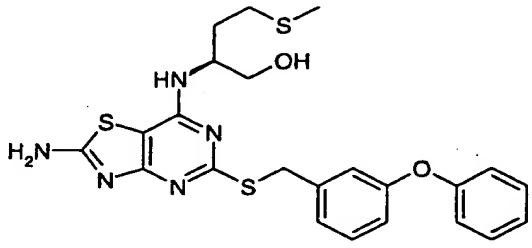
5-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-pentanol



MS: APCI (+ve) 468 (M+1)

Example 99

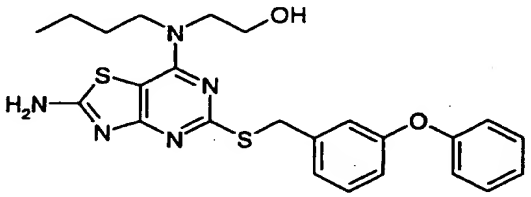
(S)-2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-4-(methylthio)-1-butanol



MS: APCI (+ve) 500 (M+1)

Example 100

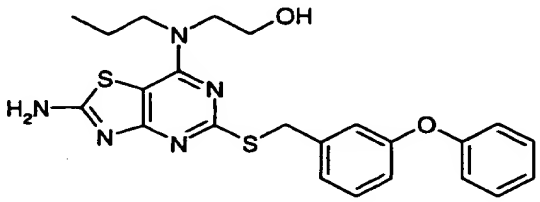
2-((2-Amino-5-((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)butylamino)ethanol



MS: APCI (+ve) 482 (M+1)

Example 101

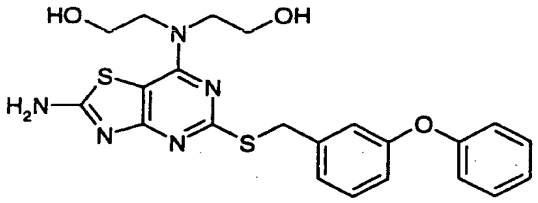
2-((2-Amino-5-((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)propylamino)ethanol



MS: APCI (+ve) 468 (M+1)

Example 102

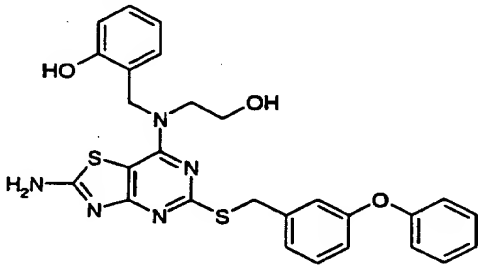
2,2'-((2-Amino-5-((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)imino)bisethanol



MS: APCI (+ve) 470 (M+1)

Example 103

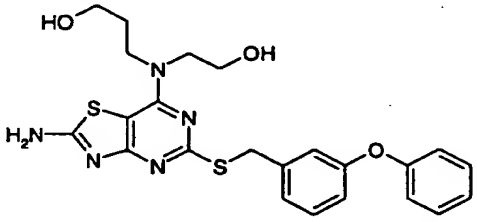
2-(((2-Amino-5-((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)(2-hydroxyethyl)amino)methyl)phenol



MS: APCI (+ve) 532 (M+1)

Example 104

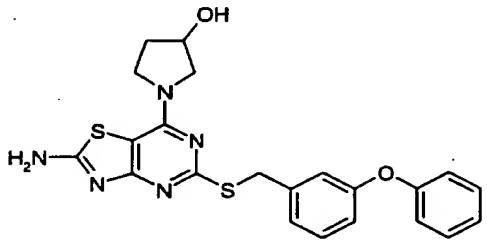
3-((2-Amino-5-((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)(2-hydroxyethyl)amino)-1-propanol



MS: APCI (+ve) 484 (M+1)

Example 105

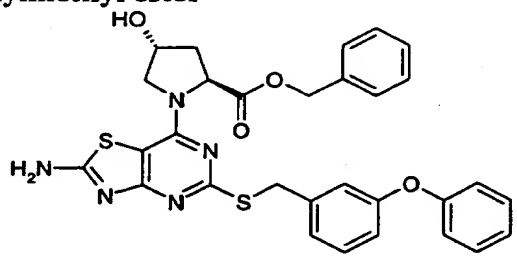
(±)-1-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-3-pyrrolidinol



MS: APCI (+ve) 452 (M+1)

Example 106

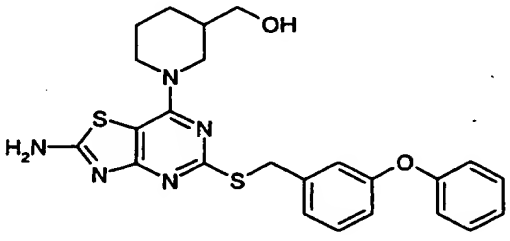
trans-1-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-4-hydroxy-L-proline phenylmethyl ester



MS: APCI (+ve) 586 (M+1)

Example 107

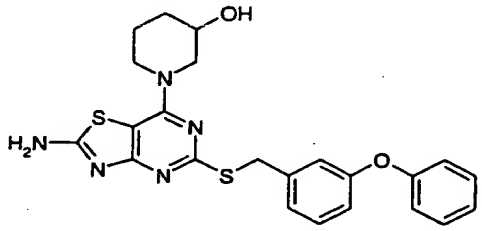
(±)-1-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-3-piperidinemethanol



MS: APCI (+ve) 480 (M+1)

Example 108

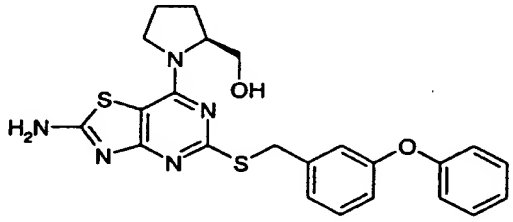
(±)-1-(2-Amino-5-((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-3-piperidinol



MS: APCI (+ve) 466 (M+1)

Example 109

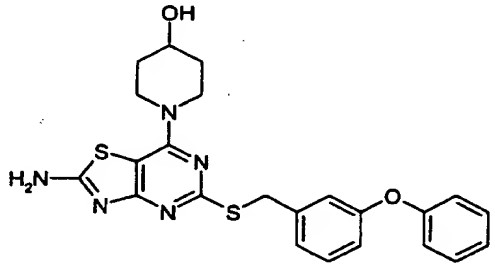
(S)-1-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-2-pyrrolidinemethanol



MS: APCI (+ve) 466 (M+1)

Example 110

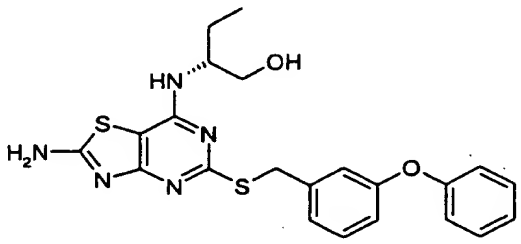
1-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-4-piperidinol



MS: APCI (+ve) 466 (M+1)

Example 111

(R)-2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol



(a) 7-chloro-5-((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-2-amine

Prepared by the method of Example1(a).

m.p. 178-180°C

MS: APCI (+ve) 401 (M+1)

^{1}H NMR: δ (DMSO) 4.37 (s,2H), 6.83-7.39 (m,9H) and 8.95 (s,2H).

(b) (R)-2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol

Prepared by the method of Example 1(b).

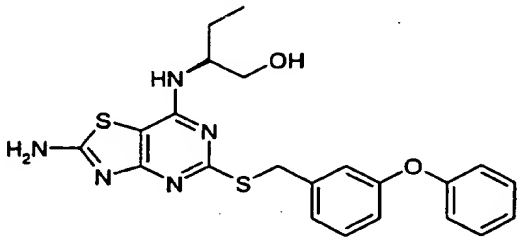
m.p. 108-111°C

MS: APCI (+ve) 454 (M+1)

^{1}H NMR: δ (DMSO) 0.81 (t,3H), 1.41 (m,2H), 1.62 (m,2H), 3.36 (m,2H), 4.03 (m,1H), 4.31 (q,2H), 4.62 (s,1H), 6.78-7.38 (m,9H) and 8.00 (s,2H).

Example 112

(S)-2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol



Prepared by the method of Example 1(b).

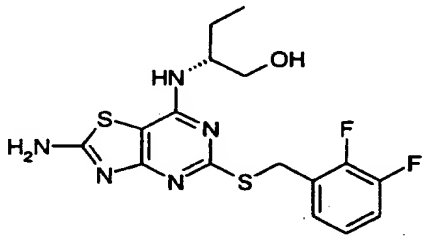
m.p. 111-114°C

MS: APCI (+ve) 454 (M+1)

^{1}H NMR: δ (DMSO) 0.81 (t,3H), 1.41 (m,2H), 1.62 (m,2H), 3.36 (m,2H), 4.02 (br d,1H), 4.32 (q,2H), 4.60 (s,1H), 6.79-7.40 (m,9H) and 8.04 (s,2H).

Example 113

(R)-2-((2-Amino-5-(((2,3-difluorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol



(a) 7-Chloro-5-(((3,4-difluorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-2-amine

Prepared by the method of Example 1(a).

m.p. 209-210°C

MS: APCI(+ve) 345/6 (M+1)

^{1}H NMR: δ (DMSO) 4.45 (s,2H), 7.10-7.42 (m,3H) and 8.90 (br s,2H).

(b) (R)-2-((2-Amino-5-(((3,4-difluorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol

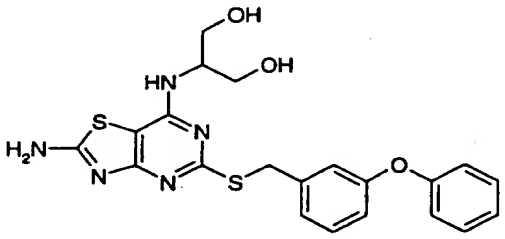
Prepared by the method of Example 1(b).

MS: APCI(+ve) 398 (M+1)

^{1}H NMR: δ (DMSO) 0.82 (t,3H), 1.34-1.71 (m,4H), 3.37 (m,2H), 4.03 (br d,1H), 4.38 (q,2H), 4.62 (t,1H), 6.96 (d,1H), 7.06-7.40 (m,3H) and 8.02 (s,2H).

Example 114

2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1,3-propanediol



Prepared by the method of Example 1(b).

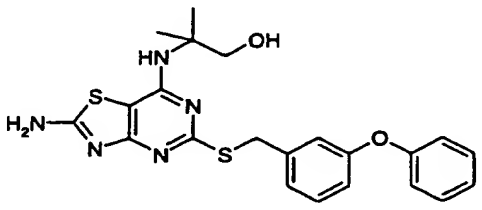
m.p. 220-222°C

MS: APCI (+ve) 456 (M+1)

^{1}H NMR: δ (DMSO) 3.50 (t,4H), 4.13 (m,1H), 4.32 (s,2H), 4.60 (t,2H), 6.78-7.40 (m,10H) and 8.01 (s,2H).

Example 115

2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2-methyl-1-propanol



Prepared by the method of Example 1(b) with 10 equivalents of amine, 45-65°C and reaction time of 3 weeks. Purification by chromatography on silica eluting with methanol/dichloromethane mixtures gave the title compound.

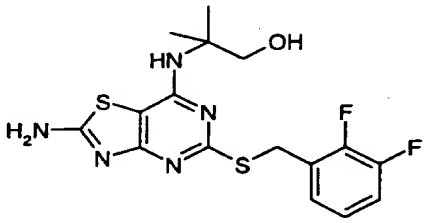
m.p. 126-130°C

MS: APCI (+ve) 454 (M+1)

^{1}H NMR: δ (DMSO) 1.30 (s,6H), 3.53 (d,2H), 4.33 (s,2H), 4.86 (t,1H), 6.28 (s,1H), 6.80-7.40 (m,9H) and 8.00 (s,2H).

Example 116

2-((2-Amino-5-(((2,3-difluorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2-methyl-1-propanol



Prepared by the method of Example 1(b) with 10 equivalents of amine, 45-65°C and reaction time of 3 weeks. Purification by chromatography on silica eluting with methanol/dichloromethane mixtures gave the title compound.

m.p. 231-234°C

MS: APCI (+ve) 398 (M+1)

^{1}H NMR: δ (DMSO) 1.30 (s,6H), 3.53 (d,2H), 4.40 (s,2H), 4.84 (t,1H), 6.32 (s,1H), 7.10-7.40 (m,3H) and 8.03 (s,2H).

Example 117

Ligand Binding Assay

[^{125}I]IL-8 (human, recombinant) was purchased from Amersham, U.K. with a specific activity of 2,000Ci/mmol. All other chemicals were of analytical grade. High levels of

hrCXCR2 were expressed in HEK 293 cells (human embryo kidney 293 cells ECACC No. 85120602) (Lee *et al. (1992) J. Biol. Chem.* **267** pp16283-16291). hrCXCR2 cDNA was amplified and cloned from human neutrophil mRNA. The DNA was cloned into PCRScript (Stratagene) and clones were identified using DNA. The coding sequence was sub-cloned into the eukaryotic expression vector RcCMV (Invitrogen). Plasmid DNA was prepared using Quiagen Megaprep 2500 and transfected into HEK 293 cells using Lipofectamine reagent (Gibco BRL). Cells of the highest expressing clone were harvested in phosphate-buffered saline containing 0.2%(w/v) ethylenediaminetetraacetic acid (EDTA) and centrifuged (200g, 5min.). The cell pellet was resuspended in ice cold homogenisation buffer [10mM HEPES (pH 7.4), 1mM dithiothreitol, 1mM EDTA and a panel of protease inhibitors (1mM phenyl methyl sulphonyl fluoride, 2μg/ml soybean trypsin inhibitor, 3mM benzamidine, 0.5μg/ml leupeptin and 100μg/ml bacitracin)] and the cells left to swell for 10 minutes. The cell preparation was disrupted using a hand held glass mortar/PTFE pestle homogeniser and cell membranes harvested by centrifugation (45 minutes, 100,000g, 4°C). The membrane preparation was stored at -70°C in homogenisation buffer supplemented with Tyrode's salt solution (137mM NaCl, 2.7mM KCl, 0.4mM NaH_2PO_4), 0.1%(w/v) gelatin and 10%(v/v) glycerol.

All assays were performed in a 96-well MultiScreen 0.45μm filtration plates (Millipore, U.K.). Each assay contained ~33pM [^{125}I]IL-8 and membranes (equivalent to ~80,000 cells) in assay buffer [Tyrode's salt solution supplemented with 10mM HEPES (pH 7.4), 1.8mM $CaCl_2$, 1mM $MgCl_2$, 0.5mg/ml bacitracin and 0.1%(w/v) gelatin]. In addition, a compound of Examples 1 to 116 was pre-dissolved in DMSO and added to reach a final concentration of 1%(v/v) DMSO. The assay was initiated with the addition of membranes and after 1.5 hours at room temperature the membranes were harvested by filtration using a Millipore MultiScreen vacuum manifold and washed twice with assay buffer (without bacitracin). The backing plate was removed from the MultiScreen plate assembly, the filters dried at room temperature, punched out and then counted on a Cobra γ-counter.

The compounds of Examples 1 to 116 were found to have IC_{50} values of less than (<) 10μM.

Example 118

Intracellular Calcium Mobilisation Assay

Human neutrophils were prepared from EDTA-treated peripheral blood, as previously described (Baly *et al.* (1997) Methods in Enzymology 287 pp70-72), in storage buffer [Tyrode's salt solution (137mM NaCl, 2.7mM KCl, 0.4mM NaH_2PO_4) supplemented with 5.7mM glucose and 10mM HEPES (pH 7.4)].

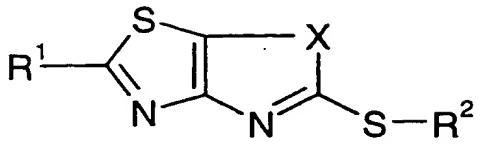
The chemokine GROα (human, recombinant) was purchased from R&D Systems (Abingdon, U.K.). All other chemicals were of analytical grade. Changes in intracellular free calcium were measured fluorometrically by loading neutrophils with the calcium sensitive fluorescent dye, fluo-3, as described previously (Merritt *et al.* (1990) Biochem. J. 269, pp513-519). Cells were loaded for 1 hour at 37°C in loading buffer (storage buffer with 0.1%(w/v) gelatin) containing 5μM fluo-3 AM ester, washed with loading buffer and then resuspended in Tyrode's salt solution supplemented with 5.7mM glucose, 0.1%(w/v) bovine serum albumin (BSA), 1.8mM $CaCl_2$ and 1mM $MgCl_2$. The cells were pipetted into black walled, clear bottom, 96 well micro plates (Costar, Boston, U.S.A.) and centrifuged (200g, 5 minutes, room temperature).

A compound of Examples 1 to 116 was pre-dissolved in DMSO and added to a final concentration of 0.1%(v/v) DMSO. Assays were initiated by the addition of an A_{50} concentration of GROα and the transient increase in fluo-3 fluorescence (λ_{Ex} =490nm and λ_{Em} = 520nm) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

Certain of the compounds of Examples 1 to 116 were tested and found to be antagonists of the CXCR2 receptor in human neutrophils.

CLAIMS

1. A compound of general formula



(I)

wherein R^1 represents a hydrogen or halogen atom, or a group $-NR^3R^4$;

R^3 and R^4 each independently represent a hydrogen atom, a C_3-C_6 cycloalkyl group, or a C_1-C_6 alkyl group optionally substituted by one or more substituents independently selected from amino, amido, hydroxyl, (di)C_1-C_6 alkylamino, C_2-C_6 acylamino, C_1-C_6 alkoxy optionally substituted by at least one hydroxyl, and morpholinyl;

R^2 represents a C_1-C_6 alkyl or C_2-C_6 alkenyl group, each of which may be optionally substituted by a phenyl or phenoxy group, the phenyl or phenoxy group being optionally substituted by one or more substituents independently selected from halogen atoms, nitro, trifluoromethyl, C_1-C_6 alkyl, C_1-C_6 alkoxy and phenoxy;

X represents a group -C(O)NH- or $-C(NR^5R^6)=N-$; and

R^5 and R^6 each independently represent a hydrogen atom, a saturated hydrocarbyl ring system containing from 3 to 7 carbon atoms optionally substituted by at least one hydroxyl group, or a C_1-C_6 alkyl group optionally substituted by one or more substituents independently selected from the group consisting of amino, hydroxyl, C_1-C_6 alkoxy optionally substituted by at least one hydroxyl, C_1-C_6 alkylthio, (di)C_1-C_6 alkylamino optionally substituted by at least one hydroxyl, and phenyl optionally substituted by one or more substituents independently selected from halogen atoms, amino and hydroxyl; or R^5 and R^6 together with the nitrogen atom to which they are attached form a pyrrolidinyl or piperidinyl ring optionally substituted by one or more substituents independently selected from hydroxyl, hydroxyC_1-C_6 alkyl and benzyloxycarbonyl; or

a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1, wherein R^1 represents a group $-NR^3R^4$.

3. A compound according to claim 1 or claim 2, wherein R^3 and R^4 each independently represent a hydrogen atom, a cyclopropyl group, or a C_1-C_6 alkyl group optionally substituted by one or two substituents independently selected from amido, hydroxyl, dimethylamino, diethylamino, acetylamino, C_1-C_2 alkoxy optionally substituted by one hydroxyl, and morpholinyl.

4. A compound according to any one of claims 1 to 3, wherein R^2 represents a C_1-C_6 alkyl group or C_2-C_4 alkenyl group, each of which may be optionally substituted by a phenyl or phenoxy group, the phenyl or phenoxy group being optionally substituted by one, two or three substituents independently selected from fluorine, chlorine, bromine, iodine, nitro, trifluoromethyl, C_1-C_4 alkyl, C_1-C_4 alkoxy and phenoxy.

5. A compound according to any one of the preceding claims, wherein X represents $-C(NR^5R^6)=N-$ and R^5 and R^6 each independently represent a hydrogen atom, a saturated hydrocarbyl ring system containing from 3 to 7 carbon atoms optionally substituted by one hydroxyl group, or a C_1-C_6 alkyl group optionally substituted by one or two substituents independently selected from the group consisting of amino, hydroxyl, C_1-C_4 alkoxy optionally substituted by one hydroxyl, C_1-C_4 alkylthio, C_1-C_4 alkylamino optionally substituted by one hydroxyl, and phenyl optionally substituted by one or two substituents independently selected from chlorine, amino and hydroxyl; or R^5 and R^6 together with the nitrogen atom to which they are attached form a pyrrolidinyl or piperidinyl ring optionally substituted by one or two substituents independently selected from hydroxyl, hydroxymethyl and benzyloxycarbonyl.

6. A compound according to claim 1 being selected from:
(R)-2-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol,
(S)-2-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol,
2-Amino-5-(((2,3-difluorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

5-(((3-Phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

(±)-2-((2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol,

2-((2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7-yl)amino)ethanol,

5-(Pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Bromo-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-((3-(Dimethylamino)propyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-((2-(Diethylamino)ethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-((2-(Dimethylamino)ethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-((3-Hydroxypropyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-((2-(Acetylamino)ethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

(±)-2-((2,3-Dihydoxypropyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-((2-(4-Morpholinyl)ethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-((2-Methoxyethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-((1-Methylethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-(Cyclopropylamino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

(±)-2-((2-Hydoxypropyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-((2-(2-Hydroxyethoxy)ethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-((2-Hydroxy-2-methylpropyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-((2-Hydroxyethyl)amino)-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

(2S,3R)-3-Hydroxy-2-((7-oxo-5-(pentylthio)-4H-thiazolo[4,5-d]pyrimidin-2-yl)-amino)butanamide,

N^7-(3-(Dimethylamino)propyl)-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine,

N^7-(2-(Diethylamino)ethyl)-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine,

N^7-(2-(Dimethylamino)ethyl)-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine,

3-((2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-propanol,

N^7-Cyclohexyl-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine,

(±)-3-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1,2-propanediol,

N^7-(2-Methoxyethyl)-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine,

5-(Pentylthio)-N^7-propylthiazolo[4,5-d]pyrimidine-2,7-diamine,

N^7-Cyclopentyl-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine,

N^7-Cyclopropyl-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine,

N^7-(2-Methylpropyl)-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine,

(±)-1-((2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2-propanol,

(exo)-N^7-Bicyclo[2.2.1]hept-2-yl-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine,

2-(2-((2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7-yl)amino)ethoxy)ethanol,

(±)-N^7-(2-Methylbutyl)-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine,

1-((2-Amino-5-(pentylthio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2-methyl-2-propanol,

N^7-((2-Aminophenyl)methyl)-5-(pentylthio)thiazolo[4,5-d]pyrimidine-2,7-diamine,

2-Amino-5-((2-phenoxyethyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

E-2-Amino-5-((3-phenyl-2-propenyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Amino-5-((3-(2,4-bis(1,1-dimethylethyl)phenoxy)propyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Amino-5-(((4-(trifluoromethyl)phenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Amino-5-(((3,5-dichlorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Amino-5-(((2,4-dichlorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Amino-5-(((3,4-dichlorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Amino-5-(((3,5-dibromophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Amino-5-(((2-nitrophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Amino-5-(((2-fluorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Amino-5-(((2-iodophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Amino-5-(((3-chlorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Amino-5-(((2-chlorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Amino-5-(((4-chloro-2-nitrophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Amino-5-(((3-chloro-4-methoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Amino-5-(((2,3-dichlorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Amino-5-(((3,5-difluorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Amino-5-(((2,4-bis(trifluoromethyl)phenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Amino-5-(((2-bromophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Amino-5-(((2,3,4-trifluorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Amino-5-(((3-bromophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

2-Amino-5-(((2-fluoro-3-methylphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7(4H)-one,

3-(2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2,2-dimethyl-1-propanol,

(±)-α-(((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)methyl)benzenemethanol,

(R)-β-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)benzenepropanol,

2-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)ethanol,

(R)-2-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-4-methylpentanol,

(±)-1-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2-propanol,

(±)-β-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-4-chlorobenzenepropanol,

(±)-3-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1,2-propanediol,

2-((2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)propylamino)ethanol,

(±)-1-(2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-3-pyrrolidinol,

(±)-1-(2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-3-piperidinol,

1-(2-Amino-5-((phenylmethyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-4-piperidinol,

3-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2,2-dimethyl-1-propanol,

(±)-2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol,

(±)-α-(((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-amino)methyl)benzenemethanol,

4-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol,

6-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-hexanol,

4-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-amino)cyclohexanol,

(R)-β-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-amino)benzenepropanol,

(±)-2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-propanol,

2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-amino)ethanol,

(R)-2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-4-methylpentanol,

(±)-1-Amino-3-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2-propanol,

(±)-1-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2-propanol,

2-(((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)methyl)-2-ethyl-1,3-propanediol,

(±)-β-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-4-chlorobenzenepropanol,

(±)-3-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1,2-propanediol,

2-((2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)ethyl)amino)ethanol,

3-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-propanol,

(±)-α-(((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)methyl)-3,4-dichlorobenzenepropanol,

1-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2-methyl-2-propanol,

2-(2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)ethoxy)ethanol,

5-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-pentanol,

(S)-2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-4-(methylthio)-1-butanol,

2-((2-Amino-5-((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)butylamino)ethanol,

2-((2-Amino-5-((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)propylamino)ethanol,

2,2'-((2-Amino-5-((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)imino)bisethanol,

2-(((2-Amino-5-((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)(2-hydroxyethyl)amino)methyl)phenol,

3-((2-Amino-5-((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)(2-hydroxyethyl)amino)-1-propanol,

(±)-1-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-3-pyrrolidinol,

trans-1-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-4-hydroxy-L-proline phenylmethyl ester,

(±)-1-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-3-piperidinemethanol,

(±)-1-(2-Amino-5-((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-3-piperidinol,

(S)-1-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-2-pyrrolidinemethanol,

1-(2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)-4-piperidinol,

(R)-2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol,

(S)-2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol,

(R)-2-((2-Amino-5-(((2,3-difluorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1-butanol,

2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-1,3-propanediol,

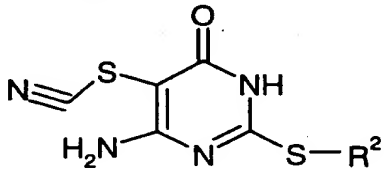
2-((2-Amino-5-(((3-phenoxyphenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2-methyl-1-propanol,

2-((2-Amino-5-(((2,3-difluorophenyl)methyl)thio)thiazolo[4,5-d]pyrimidin-7-yl)amino)-2-methyl-1-propanol,

and their pharmaceutically acceptable salts and solvates.

7. A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises:

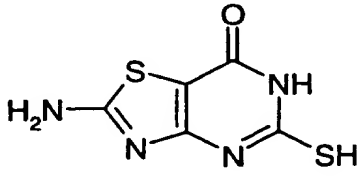
(a) when X represents -C(O)NH- and R^1 is NH_2, heating a compound of general formula



(II)

wherein R^2 is as defined in formula (I); or

(b) when X represents -C(O)NH- and R^1 is NH_2, reacting a compound of general formula



(III)

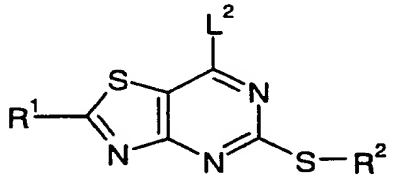
with a compound of general formula (IV), R^2 - L^1, wherein L^1 represents a leaving group and R^2 is as defined in formula (I); or

(c) when X represents -C(O)NH- and R^1 is a hydrogen atom, reacting a corresponding compound of formula (I) in which R^1 is NH_2, with a diazotizing agent; or

(d) when X represents -C(O)NH- and R^1 is a halogen atom, reacting a corresponding compound of formula (I) in which R^1 is NH_2, with a diazotizing agent and a halogenating agent; or

(e) when X represents -C(O)NH- and R^1 is a group $-NR^3R^4$, reacting a corresponding compound of formula (I) in which R^1 is a halogen atom, with a compound of general formula (V), R^3R^4NH, wherein R^3 and R^4 are as defined in formula (I); or

(f) when X represents $-C(NR^5R^6)=N-$, reacting a compound of general formula



(VI)

wherein L^2 represents a leaving group and R^1 and R^2 are as defined in formula (I), with a compound of general formula (VII), R^5R^6NH, wherein R^5 and R^6 are as defined in formula (I);

and optionally after (a), (b), (c), (d), (e) or (f) forming a pharmaceutically acceptable salt or solvate of the compound of formula (I).

8. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 6 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

9. A process for the preparation of a pharmaceutical composition as claimed in claim 8 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 6 with a pharmaceutically acceptable adjuvant, diluent or carrier.

10. A compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as claimed in any one of claims 1 to 6 for use in therapy.

11. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 6 in the manufacture of a medicament for use in therapy.

12. A method of treating a chemokine mediated disease wherein the chemokine binds to an IL-8α or β receptor, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 6.

13. A method of treating an inflammatory disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 6.

ABSTRACT

NOVEL COMPOUNDS

The invention provides certain thiazolopyrimidine compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.